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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,217	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10,19 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10,19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions/Claims/Status

Applicant's election of Group IV, claims 8, 10, 19, and 22, drawn to a small interfering RNA and composition thereof targeted to a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, without traverse, in the reply filed on 9/25/07 is acknowledged.

Also acknowledged are Applicant's amendments to the claims, filed 9/25/07. With entry of the amendment, claims 8, 10, 19, and 22 are pending and examined herein.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/414,867, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, Application No. 60/414,867 does not provide adequate written description support for claims to small interfering RNAs against

polynucleotides encoding polypeptide SEQ ID NO:16. While Application No. 60/414,867 contemplates using antisense oligonucleotides against any of a number of upregulated genes disclosed therein, including the seqeuence encoding hypothetical protein FLJ22357 (see Table 3 therein), the dislcosure does not explicitly or clearly comprehend siRNAs against FLJ22357.

Additionally, and more specifically, Application No. 60/414,867 does not describe an siRNA comprising instantly claimed SEQ ID NO:13 (claim 10).

Furthermore, Application No. 60/414,867 does not provide adequate enabling support for the use of compositions comprising siRNAs against polynucleotides encoding polypeptide SEQ ID NO:16 to treat any proliferative disease such as cancer (claims 19 and 22).

If applicant believes that support for the subject matter now claimed is present in the earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

For purposes of this examination, the earliest effective filing date of claims 8, 10, 19, and 22, with regard to the siRNA embodiments, is 7/29/2003.

Claim Objections

Claims 8, 19, and 22, are objected to for reciting non-elected subject matter. The claims recite antisense polynucleotides and non-elected targets (parts b and c of claims 8 and 19).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8, 10, 19, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Arts et al. (WO 2004/094636 A1). WO 2004/094636 A1 is over 400 pages in length, and contains a lengthy sequence disclosure. Applicants are being provided with the specification, claims, drawings, and pertinent pages of the sequence disclosure cited herein.

The instant specification teaches that "[t]he siRNA is constructed such that a single transcript (double stranded RNA) has both the sense and complementary antisense sequences from the target gene, e.g., a hairpin." See paragraph 121 of the instant pre-grant publication. Thus, the instant application recognizes the term "siRNA" embraces small hairpin RNAs as well conventional biomolecular siRNAs.

Arts et al. disclose a short interfering RNA comprising instant SEQ ID NO:13 for the inhibition of the gene corresponding to GenBank Accession No. NM_022450, encoding protein FLJ22357. See SEQ ID NO:8317 in Table 1, page 290. Image provided below.

Compare instant SEQ ID NO: 13 (gtacgtgcagcaggagaac) to SEQ ID NO:8317.

Polypeptide FLJ22357 is identical to instantly recited SEQ ID NO:16.

WO 2004/094636 **PCT/EP2003/004362**

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NM_022450	FLJ22357	8316	ACTGGCAGCGCAAGAGCATCC
NM_022450	FLJ22357	8317	ACGTACGTGCAGCAGGAGAAC
NM_022450	FLJ22357	8318	ACCCTGGCCAGTGCCATCTTC

With regard to claims 19 and 22, Arts et al. teach transfecting cells with vectors encoding the disclosed short interfering RNAs in the form of a hairpin to inhibit the target gene. Accordingly, Arts et al. teach compositions comprising small interfering RNAs identical to that now claimed. Absent evidence to the contrary, the carriers and excipients known to those of skill in the art for the formulation of the shRNAs and vectors thereof would be "pharmaceutically acceptable." Moreover, Arts et al. contemplate using the disclosed siRNAs for drug target discover, implying both in vitro and in vivo studies, which would require pharmaceutically acceptable practice (page 5). Beyond the recitation of a pharmaceutically acceptable carrier claims 19 and 22 add no other structural limitations to the claimed siRNA.

Therefore, Arts et al. taught each and every aspect of the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata, A., et al., "Homo sapiens hypothetical protein FLJ22357 similar to epidermal growth factor receptor-related protein (FLJ22357), mRNA" Genbank GI No. 11967982, Dec. 19, 2000; in view of Tuschl et al. (US 2004/0259247 A1) and Bass (2001) *Nature* 411:428-429.

The claims are drawn to a small interfering RNA targeted to a polynucleotide encoding polypeptide SEQ ID NO:16.

SEQ ID NO:16 is identical to human hypothetical protein FLJ22357. The mRNA sequence encoding polypeptide sequence FLJ22357 was known in the prior art, as shown by Kawabata et al. Similarties to epidermal growth factor receptor were also noted.

While Kawabata et al. did not teach making and using small interfering RNAs against the mRNA encoding polypeptide sequence FLJ22357, it would have been obvious to one of skill in the art at the time of invention to make and use siRNAs targeted to the mRNA encoding polypeptide sequence FLJ22357 to determine the function of the gene and further characterize the biological activities of the protein.

It is the normal desire of scientists to understand the function of every expressed protein in every cell in every species.

At the time of invention, siRNAs were universally recognized, art-accepted tools for probing gene function, using classical loss-of-function analyses (reverse genetics) to identify phenotypes associated with any given protein.

For example, Tuschl et al. taught the materials and methods for making and using siRNAs against virtually any known sequence for both research and therapeutic purposes in cells in vitro and in vivo. See entire specification, especially pages 1-7. As such Tuschl et al. represents a complete blueprint for the design and synthesis of siRNAs and application of RNAi technology for inhibiting gene expression in any mammalian cell. At paragraph 29 therein, Tuschl et al. taught that the method [RNAi] may be used for determining the function of a gene in a cell or an organism. At paragraph 30, it is said that by by inhibiting the function of a gene valuable information and therapeutic benefits in the agricultural field or in the medicine or veterinary medicine field may be obtained.

Bass also taught the advantages of RNAi for gene function research, stating that "Once the sequence of a gene is known, RNAi offers a quick and easy way to determine its function, and the technique is accessible to a scientist in a small lab, as well as to a consortium attempting to assign function to the genes of an entire chromosome" (page 428, left column).

Accordingly, one of skill in the art would have considered it obvious at the time of invention to make and use siRNAs to any known gene, including the polynucleotide(s) recited in the instant claims, as a tool to investigate and/or further characterize the function of the gene. Knockdown is but one type of investigative tool the skilled practitioner would turn to during the

course of any study designed to determine the biological function of a gene. At the time, RNAi was known to be readily accessible and highly potent method for knocking down the expression of a gene and thereby for probing the essential or non-essential nature of gene.

Thus, the use of RNAi as a tool to determine gene function is suggested and taught by the prior art (Tuschl et al. and Bass, for example). The polynucleotide encoding FLJ22357 (i.e., SEQ ID NO:16) was known in the prior art (Kawabata et al.). See also the paragraph 205 of the instant pre-grant publication, which acknowledges SEQ ID NO:15 is identical to GenBank NM_022450. Therefore, for all these reasons, one of skill would have been both well motivated and have had reasonable expectation of success in making and using siRNAs against polynucleotides encoding instant SEQ ID NO:16.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to siRNA-containing compositions for treating a cell proliferative disease, such as cancer.

The "pharmaceutically effective amount" and "pharmaceutically acceptable carrier" language in combination with the intended use recited in the preamble for treating a cell proliferative disease requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for treating any proliferative disease, particularly cancer.

Neither the specification nor the prior art provide adequate representation of the claimed use for treating proliferative disease in vivo using the claimed composition. While the specification shows inhibition of the target gene in K562 cells in vitro slows cell growth, and

expression of the target gene enhances cell growth in an immortalized cell line, these data are not readily extrapolated to treatments of proliferative disease in vivo. The data merely show that the gene may be required for cell division, not that it is an oncogene per se. Cancer is a multifactorial process. More would be required before one of skill in the art would be able to use the claimed compositions in the manner intended to selectively treat abnormal cell division in vivo. Many genes are involved in cell division. While overexpression of the instant gene may spur cell growth, many genes when overexpressed may alter cell division. Similarly, many different genes when underexpressed may slow cell growth. A nexus has not been established reasonably linking the target gene with proliferative disease in a living organism. No evidence, direct or indirect, has been provided to lead one of skill in the art to believe that providing the claimed composition to a mammal affected proliferative disease would provide a treatment effect, wherein the diseased cells are selectively targeted and inhibited.

Additionally, problems related to the pharmaceutical use of siRNAs and antisense nucleic acids were well known in the art at the time of invention. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Hannon and Rossi (2004) *Nature* 431:371–378 teach that, while RNAi has the potential to be exploited therapeutically, and despite early proofs of principle, "there are important issues and concerns about the therapeutic application of this technology, including difficulties with delivery and uncertainty about potential toxicity." (page 374, 2nd column) "Two key challenges in developing RNAi as a therapy are avoiding off-target effects and ensuring efficient delivery." (page 377, 1st column) "The issue of delivery has restricted the antisense field for almost two

decades. It is feasible to infuse backbone-modified oligonucleotides *in vivo*, but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissue types is still not a practical reality for oligonucleotide-based therapeutics." (page 377, 2nd column) "As with HIV therapeutics, delivery of the siRNAs or shRNA vectors is the main challenge for successful treatment of HCV. The method of delivery used in several *in vivo* studies—hydrodynamic intravenous injection—is not feasible for the treatment of human hepatitis." (page 376) "However, enhancing siRNA stability is not enough unless the siRNAs can penetrate cells and tissue *in vivo* in concentrations sufficient to be therapeutically functional. As siRNAs are double-stranded molecules, delivery and cellular uptake is more of a challenge than for single-stranded antisense agents, which bind to serum proteins and are taken up by cells and tissues *in vivo*. There are a few reports of functional RNAi being obtained by systemic delivery of liposome-encapsulated siRNAs,..." (page 376) "Systemic delivery of siRNAs to T lymphocytes is probably not feasible owing to the immense number of these cells. Using viral vectors to deliver anti-HIV-encoding shRNA genes is also problematic, and systemic delivery is not yet practicable because the immunogenicity of the vectors themselves precludes performing multiple injections." (page 375)

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the compositions to treat cell proliferative diseases in any organism, mammal, or

human subject. Instead, the specification makes general assertions that one of skill in the art would know how to apply (dose, frequency, and duration) the antisense oligos to the lungs (pages 32-34, for example). Examples of in vivo use of the pharmaceutical compositions, working or otherwise, are not provided.

Cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to cells in any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by

the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" language from the instant claims and amending the preamble to remove language directed to the treatment of disease would overcome this rejection. The rejection is not to the compositions per se but to the intended use and characterization of the compositions as pharmaceuticals.

Art made of record but not currently relied on

The following art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Nakamura et al. (US 2006/0210576 A1), though now abandoned, would be considered pertinent to the instant claims if revived inasmuch as Nakumura et al. contained claims, claims 15-17, to a composition for treating a metastatic lesion of colorectal cancer or preventing metastasis of colorectal cancer in a subject, comprising a pharmaceutically effective amount of a small interference RNA against one or more genes selected from the group consisting of MLXs 1-153. MLX 44, disclosed in Table 1 at page 1 of the specification, corresponds to hypothetical protein FLJ22357, identical to instant nucleic acid SEQ ID NO:15.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, AU 1635
November 15, 2007